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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

ALLEN, MARIANNE P

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/923,870

Applicant(s)

PALSSON, BERNHARD

Examiner

Marianne P. Allen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/20/04 and 1/21/05.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 49-65 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 49-65 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's arguments filed 1/21/05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 53, 54, 61, and 65 are objected to because of the following informalities: At least these claims contain a typographical error, "*in silco*." It appears that "*in silico*" was intended. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 49-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and/or as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is both a new matter and enablement rejection.

Claim 49 has been amended to recite "obtaining a DNA sequence of a genome." As set forth in the prior Office action, the specification contemplates obtaining the entirety of the genome and not "a DNA sequence" or partial sequence. See page 7, line 5. This amendment is considered to be new matter.

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Claim 53 remains new matter for failing to perform flux balance analysis to produce the *in silico* representation of the microbial organism. Applicant's arguments are not persuasive. The disclosure on pages 6-8 in describing Figure 2 at state 64 is the flux balance analysis (FBA) and not any type of general linear programming problem. The specification does not appear to contemplate a more generic method of combining the metabolic demand and uptake rate with the stoichiometric matrix to produce an *in silico* representation. Applicant points to pages 10-11 and discusses metabolic capabilities of the representation. The flow chart in Figure 2 includes this step and the specification does not contemplate a method paralleling Figure 2 absent this step. The specification describes a method of producing an *in silico* microbial strain from the metabolic genotype. Applicant argues a distinction between "metabolic phenotype" and "representation." The specification does not contemplate a "representation" that is limited as argued by applicant. The specification contemplates producing the metabolic phenotype. Applicant is again requested to point to basis in the specification for the preamble goal and produced with the steps as presently written.

Basis for the methods of claims 57-61 is still not seen, particularly repeating steps a) to d) and providing only metabolic genes (as opposed to selecting the subset that are metabolic genes from the ORF's found in the whole genome). Applicant's arguments are not persuasive. The specification does not contemplate the iterative procedure set forth in the claims. There is no disclosure of performing the method on a gene by gene basis. Applicant appears to be arguing that the various portions of the specification pointed to make this an obvious way to perform the method. This is insufficient to meet the written description requirement. See *Lockwood v. American Airlines, Inc.* 41 USPQ 2d 1961 at 1966 (CAFC, 3/4/97).

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The specification as originally filed would not reasonably convey to one of ordinary skill in the art that the invention as presently claimed was contemplated.

To the degree that claim 49 is intended to assign function to every open reading frame identified in the microbial genome, the specification is not enabling for the reasons set forth in the prior Office action. The declaration under 37 CFR 1.132 filed 12/20/04 is insufficient to overcome the rejection of claims 49-65 based upon 35 USC 112, first paragraph, as set forth in the last Office action.

The Subramanian declaration admits in paragraph 4 that all open reading frames in a genome cannot be automatically assigned function. However, the claims require assignment of function to all open reading frames. There is no provision for assigning only those with a certain (unspecified) level of homology to known proteins. The claims require assignment of function to all, not some, open reading frames.

Paragraph 8 of the declaration discusses assigning gene function for *E. coli*, in particular. However, the claims are directed to any microbe not just *E. coli*.

With respect to paragraph 10, there is no evidence presented in support of the assertion that "any experimentation necessary to obtain a sequence homology search and assign a function based on homology to a known gene was predictable and routine." The remainder of the paragraph outlines that criteria are selected by the user and an assertion of common practices with regard to E-values. These criteria and E-values are not limitations of the claims. Nor does this establish that the art at the time of the invention had known or accepted criteria by which function was assigned.

The totality of the declaration supports the conclusion that assignment of function was subjective. To the degree that the declaration attempts to answer the ultimate legal question of enablement and undue experimentation, this declaration is an opinion declaration and given no weight in the absence of evidence in support of the assertions.

Again, claims 49 and 57 require being able to discriminate between a metabolic gene and a non-metabolic gene. One must be able to determine those ORFs “involved in cellular metabolism” by their assigned function. However, this does not clearly demarcate those genes or ORFs intended to be included or excluded. Page 8 provides a non-limiting list as to what was intended and the degree of “involvement” is not made clear. As such, one of ordinary skill in the art would not have known exactly which sequences to include or exclude, with the exception of claims 51 and 59. From the perspective that any gene can affect the overall function of the cell, most, if not all, genes could be considered to be involved in cellular metabolism. Applicant’s arguments do not address the fact that the specification disclosure of the metes and bounds of “metabolic gene” is non-limiting and applicant does not provide a limiting definition well-known to one of ordinary skill in the art at the time of the invention for a “metabolic gene.”

Again as set forth in the prior Office action, the specification does not provide guidance on how assignment of function would then provide the metabolic reaction of the candidate metabolic gene. That is, assigning the function of a kinase based upon homology does not provide the substrate and product of the reaction. The specification provides absolutely no guidance as to how these should be determined. While page 8, discusses reviewing biochemical literature and available experimental data, this is considered to require undue experimentation

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given the breadth of the claims which are directed to any microbe and appear to embrace all genes of the microbial genome. Applicant attached the Table of Contents from Stryer et al.; however, the claims are not limited to glycolysis or particular known pathways. The claims are not limited to known substrates and products.

Claim 54-55 and 64-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 lacks antecedent basis for "metabolic demands" in claim 54.

Claim 63 lacks antecedent basis for "metabolic demands" in claim 61.

Claims 54 and 65 are confusing for reasons of record. Applicant's arguments about the *in silico* representation as distinguished from the metabolic genotype or metabolic system are not persuasive for the reasons set forth above with respect to new matter. In addition applicant's arguments admit that the methods of claims 53 and 61 are not further limited by claims 54 and 65. That is, these are directed to different methods as the flux balance step does not further define the *in silico* representation. That is, these are methods of using the *in silico* representation to do something else.

Claim Rejections - 35 USC § 102

Claims 49-51, 53-59, and 61-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Schilling et al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

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This rejection is maintained for reasons of record. As the claims as presently written embrace new matter, applicant is entitled to only the instant filing date of 8/6/01 and not the filing date of parent application 09/243,022.

Claim Rejections - 35 USC § 103

Claims 52 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schilling et al. al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

This rejection is maintained for reasons of record. Schilling remains valid prior art.

Claims 49-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Blattner et al. (Science, 1997, of record), Pennisi (Science, 1997), Edwards et al. (Abstracts of Papers, American Chemical Society, 213(1-3):BIOT 50, San Francisco, April 13-17, 1997), and Pramanik et al. (Biotechnology and Bioengineering, 1997, of record).

This rejection is maintained for reasons of record.

Applicant argues that Pramanik et al. teaches away from using models that are not produced from existing biochemical information. Applicant's response at page 17 references page 3. There is no page 3 in the Pramanik et al. reference and page 3 of the specification does not discuss this reference. It is unclear why applicant believes this reference teaches away. Applicant further argues that Edwards et al. appears to describe a comparative flux balance analysis based on "hypothesized" metabolic pathways that do not use biochemical information. This is not persuasive as Edwards et al. discloses flux balance analysis of a metabolic network

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for *H. influenzae* based on homology of putative proteins with those encoded by the known part of the *E. coli* genome. Thus, the information is rooted in known biochemical information.

It would have been obvious to produce a stoichiometric matrix and *in silico* model of the microbes *E. coli* and *H. influenzae* according to Pramanik et al. using the known genome sequence, ORFs, and metabolic genes for these microbes as disclosed by Blattner et al. and Pennisi et al. (where function has been assigned by using homology and tools such as BLAST). Such models clearly would have been of interest and within the skill of the art to produce as seen by Edwards et al. One would have been motivated to produce the stoichiometric matrix and *in silico* model in order to better understand microbial metabolism and provide more robust models of metabolism. The art applied is analogous and looks to further characterize the same microbial metabolic systems. It is maintained that it would have been obvious to combine the teachings of the prior art in order to arrive at the claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Thursday, 5:30 am - 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Marianne P. Allen
Primary Examiner
Art Unit 1631
5/2/05

mpa